REMARKS/ARGUMENTS

Claims 58-70 are pending in the instant application.

Applicants note and appreciate the withdrawal of the earlier objections and the enablement rejection under 35 U.S.C. §112, first paragraph. The remaining rejections under 35 U.S.C. §112, first paragraph and 35 U.S.C. §102 are addressed below.

I. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62 and 69-70 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the recited variant polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:59, wherein the polypeptide induces chondrocyte re-differentiation.

Applicants submit that Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO363 polypeptide induces chondrocyte re-differentiation. The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO363 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

The Examiner asserts that, "Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The compound itself is required." (Page 7 of the instant Office Action). In support of this assertion, the Examiner cites the cases of *Fiers v. Revel* (25 U.S.P.Q.2d. 1601 (Fed. Cir. 1993). and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 U.S.P.Q.2d. 1016 (Fed. Cir. 1991).

Applicants submit that *Fiers v. Revel* and *Amgen v. Chugai* addressed conception and the written description requirement in the context of DNA-related inventions. The *Amgen* court held that conception of a DNA invention "has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated." 927 F.2d 1200 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991), at 1206. The *Fiers* court extended this decision into the written description arena, holding that "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." *Fiers*, 984 F.2d at 1171. Since the instant claims are directed to polypeptides, *Fiers* and *Amgen* are distinguished on the facts and do not apply.

More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in *Enzo* was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

Accordingly, current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities. The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[1] As discussed above, Applicants have recited structural features, namely, 80% sequence identity to SEQ ID

[1] M.P.E.P. §2163 II(A)(3)(a).

NO:59, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific activity for the polypeptide, wherein the polypeptide induces chondrocyte re-differentiation. Accordingly, a description of the claimed genus has been achieved.

The Examiner asserts that "the specification does not disclose any variants of the PRO363 polypeptide(SEQ ID NO:59) which can induce chondrocyte redifferentiation. One cannot describe what one has not conceived." (Page 7 of the instant Office Action). In support of this assertion, the Examiner relies on *Fiddes v. Baird* (30 U.S.P.Q.2d 1481 at 1483). In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad claim where the specification only provide the bovine sequence.

Applicants respectfully submit that the present application is different from *Fiddes v. Baird*. In *Fiddes v. Baird.*, a common structure features, such as the sequence similarity, was not provided for the claimed genus. In contrast, Claims 58-62 clearly define both common structural features (sharing at least 80%, 85%, 90%, 95%, and 99% sequence identity to a known sequence) and functional limitations (ability to induce chondrocyte redifferentiation) of the claimed genus. Therefore, the holding in *Fiddes v. Baird.* does not apply to the present claims.

The Examiner asserts that "the only factors present in the claims are a partial structure in the form of a recitation of percent identity, and a requirement that the polypeptide can induce chondrocyte re-differentiation. **There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function (induction of chondrocyte redifferentiation).**" (Page 7 of the instant Office Action, emphasis in original).

Applicants respectfully submit that the U.S.P.T.O. Written Description Guidelines do not require a structure-function relationship. As stated by the Examiner, page 8 of the Written Description Guidelines notes five factors provided for analysis for compliance with the written description guidelines: a) partial structure; b) physical and/or chemical properties; c) functional characteristics; d) known or disclosed correlation between structure and function; e) method of making; and f) combinations of any of these factors. A structure-function correlation is only one possible factor. A combination of other factors, such as partial structure, functional characteristics, and method of making, all of which are disclosed for the instantly claimed variants, is also sufficient to provide written description.

Applicants further point out that this particular combination of functional activity and structural homology, as disclosed in the specification, has been recognized by the USPTO as

sufficient to describe a claimed genus of polypeptides. The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the claimed variant polypeptides are well known in the art and described in the specification. An assay for detecting the recited functional activity of the variant polypeptides is provided in Example 126. Finally, the claimed variant polypeptides possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:59. Accordingly, the claimed polypeptide variants meet the standards set forth in the Written Description Guidelines.

Withdrawal of the written description rejection of Claims 58-62 and 69-70 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

II. Claim Rejections Under 35 U.S.C. §102

The rejection of Claims 58-70 under 35 U.S.C. §102(e) as allegedly being anticipated by Holtzman *et al.*, U.S. 2002/0055139 A1, with priority to May 14, 1999, is maintained. Holtzman *et al.* teach a polypeptide (human A236 protein) that is 100% identical to SEQ ID NO:59.

In their Response filed November 1, 2005, Applicants submitted a Declaration under 37 C.F.R. §1.131 by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood that establishes that Applicants had cloned and sequenced SEQ ID NO:59, and determined the homology of the encoded polypeptide (SEQ ID NO:59) to the cell surface protein HCAR, before the prior art date of May 14, 1999. Applicants also explained that, as decided in cases such as *In re Stempel* and *In re Moore*, an applicant need only show that portion of his claimed invention that appears in the cited reference to support the priority claim.

The Examiner states that the Declaration under 37 C.F.R. § 1.131 filed November 1, 2005 has not been considered because it is unsigned.

There exists a corresponding application, U.S. Application Serial No. 09/978,564, filed October 16, 2001, directed to antibodies that bind PRO363. In this application, the Examiner has asserted that "the evidence submitted does not show that the applicant possessed as much of the invention as is shown in the reference." In particular, the Examiner asserts that "Holtzman also teaches that the A236 sequence (which is identical to the claimed PRO363 sequence) is expressed in a number of specific tissues including: brain, placenta, uterus, ovaries, intestinal tract and the heart...Holtzman also teaches expression of the A236 polypeptide in 293T cells." (Page 4 of the Office Action mailed February 22, 2006 for 09/978,564). In a telephone conversation, the Examiner confirmed that these arguments would also apply to the instant application; thus they are addressed here.

Applicants respectfully submit that while Holtzman may teach expression of A236/PRO363 in a number of specific tissues, it does not teach, nor does the PTO explain, how this expression leads to a practical utility. Applicants note in particular that Holtzman does not indicate that A236/PRO363 is expressed in tissues associated with any diseases or conditions; therefore, this data does not demonstrate utility for A236/PRO363 in the diagnosis or treatment of any specific diseases. As the court held in *In re Moore*,

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 U.S.P.Q. at 267 (emphasis added).

Consequently, based on the holdings of *In re Stempel* and *In re Moore*, Applicants respectfully submit that Holtzman *et al.* is not prior art under any section of 35 U.S.C. §102 since its effective priority date is after the invention by the Applicants for patent, and Holtzman *et al.* does **not** disclose any utility not found in Applicants' priority document.

Nonetheless, and without acquiescing to the Examiner's arguments, Applicants submit herein a showing that PRO363 tested positive in an assay of stimulatory activity in the proliferation of rat utricular supporting cells (Assay #54, Example 116), and that this assay was completed prior to the date of the reference. This assay is used to find agents that are potent mitogens for inner

ear supporting cells which are auditory hair cell progenitors. Such agents are useful for inducing the regeneration of auditory hair cells and treating hearing loss in mammals.

Proliferation of supporting cells in the inner ear is the major early event occurring during hair cell regeneration after acousetic trauma or aminoglycoside treatment. Because the supporting cells of the inner ear epithelium are most likely the progenitor cells for the hair cells, the proliferation of the supporting cells is critical for the replacement of the lost hair cell and supporting cells that are capable of converting into new hair cells.

Applicants submit that Assay 54, the rat utricular supporting cell proliferation assay, was developed by Zheng *et al.* as early as 1997, and was considered in the art as a rapid and reliable approach for the measurement of proliferation of progenitor cells and for identifying new mitogenic agents for treating hearing loss. (Zheng *et al.*, *J Neurosci.* 17(1):216-26 (1997); copy enclosed).

Zheng *et al.* considered this assay as "a rapid, reliable tritiated thymidine assay for measurement of the progenitor cell DNA synthesis in purified, partially dissociated postnatal rat inner ear epithelial cell cultures." (See page 217, column 1). Using this rapid, convenient assay, Zheng *et al.* examined the effects of a panel of 30 growth factors on the proliferation of utricular supporting cells. These included known and commonly studied mitogens and differentiating and survival factors in the nervous system. Zheng *et al.* discovered that several FGF family members, IGF-1, IGF-2, TGF-α, and EGF, are mitogens for the utricular supporting cells. Among them, FGF-2 is the most potent mitogen. These results were confirmed by BrdU immunocytochemistry. Inclusion of neutralizing antibodies against FGF-2 or IGF-1 in the medium reduced utricular epithelial cell proliferation. Thus, these results suggest that FGF-2 and IGF-1 are candidate molecules regulating proliferation of the inner ear supporting cells. In particular, FGF-2 is a physiological growth factor during regeneration of new hair cells following challenge by aminoglycosides or noise.

In order to confirm that this culture system represents a population of utricular supporting cells, Zheng *et al.* examined the expression of the cell surface markers typical for the supporting cells via immunocytochemical staining. Immunocytochemical staining with different types of cell markers revealed that these cultured cells expressed epithelial cell antigens, including a tight junction protein (ZO1), F-actin, and cytokeratin. They did not express antigens for other types of cells, such as glial filament protein (GFAP), the oligodendrocyte antigen (myelin), neurofilament

protein, or fibroblast antigens, vimentin and Thy1.1. (See Table 1 and page 219, column 1). Accordingly, these results suggest that the cultured cells are pure epithelial cells, and that the vast majority of the surviving cells in the cultures represented a population of utricular supporting cells.

Zheng *et al.* concluded that, "we have established a purified mammalian utricular epithelial cell culture, which allows us to rapidly examine possible effects of known and novel growth factors on supporting cell proliferation, an early phase during normal development and regeneration of new hair cells." (See page 226, column 2). Accordingly, the proliferation of rat utricular supporting cells assay disclosed in Example 116 of the instant specification is an art-recognized assay for the identification of molecules that are mitogens for inner ear supporting cells, and the results of this assay demonstrate utility for PRO363, for example, in the treatment of hearing loss.

Applicants respectfully submit a new Declaration under 37 C.F.R. §1.131 by Dr. Desnoyers, Dr. Filvaroff, Dr. Gao, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood. This Declaration establishes that Applicants had cloned and sequenced SEQ ID NO:59, and determined the homology of the encoded polypeptide (SEQ ID NO:59) to the cell surface protein HCAR, before the prior art date of May 14, 1999. In addition, the Declaration establishes that Applicants had tested PRO363 and demonstrated its ability to stimulate the proliferation of rat utricular supporting cells prior to May 14, 1999. The consideration of the Declaration is respectfully requested.

As explained in the Declaration, the proliferation of rat utricular supporting cells assay is performed as follows. Rat UEC-4 utricular epithelial cells are aliquoted into 96 well plates with a density of 3000 cells/well in 200 ul of serum-containing medium at 33°C. The cells are cultured overnight and are then switched to serum-free medium at 37°C. Various dilutions of PRO polypeptides (or nothing for a control) are then added to the cultures and the cells are incubated for 24 hours. After the 24 hour incubation, 3H-thymidine (1 uCi/well) is added and the cells are then cultured for an additional 24 hours. The cultures are then washed to remove unincorporated radiolabel, the cells harvested and counts per minute (cpm) per well determined. Cpm of at least 30% or greater in the PRO polypeptide treated cultures as compared to the control cultures is considered a positive in the assay.

Copies of pages from an internal database showing the positive results for the PRO363 polypeptide (SEQ ID NO:59), identified by Pin number PIN665-1, in Assay #54 are attached to the Declaration (with dates redacted) as **Exhibit B**. These experiments were performed and the results were obtained in the United States prior to May 14, 1999.

Exhibit B clearly shows that the polypeptide designated PRO363 was tested, and its ability to stimulate the proliferation of rat utricular supporting cells was determined prior to May 14, 1999. The column headed "mean" shows that addition of the PRO363 polypeptide to the rat utricular supporting cells resulted in an increase in proliferation of 37.1-51.9% as compared to control. This meets the standard (at least 30% as compared to control) considered to be a positive in this assay. As PRO363 has a positive response, it is a potent mitogen for inner ear supporting cells which are auditory hair cell progenitors, and thus is useful for inducing the regeneration of auditory hair cells and treating hearing loss in mammals. Accordingly, the results of the proliferation of rat utricular supporting cells assay demonstrate utility for PRO363, for example, in the treatment of hearing loss. This utility was demonstrated prior to May 14, 1999, the priority date of the Holtzman reference.

Therefore, the above Declaration clearly establishes that Applicants had not only cloned and sequenced SEQ ID NO:59, and determined the homology of the encoded polypeptide (PRO363) to the cell surface protein HCAR prior to May 14, 1999, but had also identified a practical utility for PRO363 as a mitogen for inner ear supporting cells prior to May 14, 1999. Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that Applicants have disclosed all that the cited reference discloses before the priority date of the cited reference.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Holtzman *et al.* is not prior art under §102(e) since its effective priority date is after the invention by the Applicants for patent.

In view of the foregoing arguments, withdrawal of the rejection of Claims 58-70 under 35 U.S.C. §102(e) over Holtzman *et al.* is respectfully requested.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C24**).

Respectfully submitted,

Date: July 24, 2060

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